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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IMPLANTABLE BIOABSORBABLE ARTICLE

(57) Abstract

An implantable bioabsorbable article for the separation and regeneration of tissue at a tissue defect site. The article comprises a fibrous matrix laminarly affixed to one surface of a cell-barrier sheet material. When implanted it allows ingrowth of tissue into the fibrous matrix side of the material; simultaneously the tissue to be regenerated at the tissue defect site is separated from the ingrowing tissue by the cell-barrier sheet material. A method for making the implantable bioabsorbable article is also described.

IMPLANTABLE BIOABSORBABLE ARTICLE

FIELD OF THE INVENTION

This invention relates to an implantable bioabsorbable article for use as a mammalian-cell-barrier to aid in the regeneration of tissue.

BACKGROUND OF THE INVENTION

A preferred technique to promote the regeneration of mammalian tissue is accomplished by the separation and isolation of a particular type of tissue to be regenerated from other competing undesirable tissues through the use of a biocompatible barrier material. This concept is known as guided tissue regeneration and was described in an article by J. Gottlow, et al., titled "New Attachment Formation in the Human Periodontium by Guided Tissue Regeneration" (Journal of Clinical Periodontology, 1986; Vol. 13, pp. 604-616). The function of the barrier material is to substantially preclude the movement of tissue cells through the thickness of the material and consequently limit the varieties of cell types at the treatment site. This function is combined with the requirement that the material maintain sufficient space adjacent to the defect so as to allow for the regeneration of the desirable tissue into that space. The preservation of space between the surface of the defect and the desired contours of the subsequently regenerated surface is necessary in order to allow for the regeneration of tissues into that space. Specific periodontal structures which may be regenerated in this fashion are the periodontal ligament, bone and cementum. The barrier material allows propagation of bone and periodontal ligament cells by precluding epithelial cells and gingival connective tissue cells which are believed to propagate at a greater rate. This concept may be useful for other applications where separation of specific cell varieties is desirable such as, for example, nerve repair and nerve guidance applications, bone regeneration and prevention of soft tissue adhesions, particularly those of the peritoneum.

A description of a bioabsorbable tubular device useful for nerve repair is provided in U.S. Patent 4,870,966 to Dellon, et al.

Additionally, it has been proposed that the mechanical stability of the blood clot which forms in the defect space adjacent to the

Another material that is commercially available for use in guided tissue regeneration is Vicryl Periodontal Mesh available from Johnson & Johnson. The Vicryl Periodontal Mesh is comprised of woven fibers made from a bioabsorbable copolymer of about 90% glycolide and 10% lactide. Studies have shown that the Vicryl Periodontal Mesh has had some success as a barrier material that provides for tissue regeneration (Fleisher et al., "Regeneration of lost attachment apparatus in the dog using Vicryl Absorbable Mesh", International Journal of Periodontics and Restorative Dentistry 2/1988 pp 45-55). Difficulties with this conventional woven construction include its inferior ability to maintain space adjacent to the defect and its marginal effectiveness as a tissue barrier because of the inherent porosity of the woven structure. This material is a single layer material of woven construction that is intended to both promote tissue ingrowth and simultaneously serve as a tissue barrier. As these are somewhat contradictory objectives for a single layer material of woven construction having a degree of inherent porosity, ingrowth can only be made to occur at the expense of the barrier function. The effectiveness of this material is therefore a compromise between the material's ability to allow for tissue ingrowth and the requirement to simultaneously function as a tissue barrier.

There remains a need for a bioabsorbable material for use as an effective cell-barrier that allows for tissue attachment on at least one surface, adds to the stability of the healing wound through blood infiltration and coagulation into the material, substantially precludes passage of tissue cells through the material, possesses adequate rigidity to ensure preservation of the desired space proximal to the defect and has acceptable surgical handling properties and strength.

Bioabsorbable materials are herein defined as those materials of either synthetic or natural origin which when placed into a living body are degraded through either enzymatic, hydrolytic or other chemical reactions, into byproducts which are either integrated into or expelled from the body.

Cells and tissue are herein defined as mammalian cells and mammalian tissue.

Figure 6 is a cross section of a periodontal defect showing the preferred periodontal repair embodiment of the present invention.

Figure 7 shows a schematic drawing of the process of making the implantable bioabsorbable article of the present invention.

Figure 8 shows a schematic drawing of a process of making the alternative embodiment having a fibrous matrix affixed to both sides of the cell-barrier sheet material.

Figures 9 and 10 show a schematic drawings of two alternative processes of making the implantable material of the present invention.

Figure 11 shows the implantable bioabsorbable article of the present invention formed into a tube useful for repairs such as vascular and nerve guide repair.

Figure 12 shows a cross section of an alternative tubular embodiment.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to the present invention, examples of which are illustrated in the drawings.

The basic structure of the article is shown in Figure 1, comprising a composite material having a fibrous matrix 10 laminarly affixed to a cell-barrier sheet material 12. The fibrous matrix and cell-barrier sheet material are designed to be superimposed and affixed together in a laminar fashion so that the implantable bioabsorbable article has one surface that provides an open structure of void spaces capable of accommodating tissue ingrowth while the opposite surface provides a cell-barrier.

The cross section of Figure 2A shows the implantable bioabsorbable article in further detail. The cell-barrier sheet material 12 has two opposing surfaces, designating the first opposing surface 13 and the second opposing surface 15. The fibrous matrix 10 is laminarly affixed to the first opposing surface 13 of the cell-barrier sheet material 12. By laminarly affixed is meant that the fibrous matrix 10 is attached directly to the surface of the cell-barrier sheet material 12 as shown by Figure 2A, or extends through the first opposing surface 13 as shown by the cross section of Figure 2B, or extends through the first surface 13 to the second surface 15

bioabsorption of the article has occurred. When evaluated, if mammalian cells, fibrous connective tissue cells or extracellular matrix, or collagen, have invaded the spaces between adjacent structures within the fibrous matrix, resulting in a connection between the article and adjacent tissue, the article is deemed capable of allowing tissue ingrowth and incapable of substantially precluding cell passage and ingrowth.

The cell-barrier sheet material should be composed of a synthetic bioabsorbable material such as, for example, polycaprolactone, poly p-dioxanone, trimethylene carbonate, polyglycolic acid (PGA) or polylactic acid (PLA) or copolymers thereof. For periodontal applications, a preferred material is a copolymer of PLA and PGA, with preferred mixtures ranging from about 85% PLA and 15% PGA to about 50% PLA and 50% PGA. The equal ratio copolymer can be expected to bioabsorb at the fastest rate. For a comparison of bioabsorption rates of these materials, see Lewis, Danny H., Controlled Release of Bioactive Agents from Lactide/Glycolide Polymers, pp 1-41, Biodegradable Polymers As Drug Delivery Systems, Mark Chasin and Robert Langer (ed); Marcel Dekker, Inc., New York, NY, 1990.

Copolymers of PLA and PGA are polymerized from appropriate proportions of lactide and glycolide which are cyclic dimers based on lactic acid and glycolic acid respectively. The lactic acid components of the lactide dimer may be of either the d (dextrorotatory) or l (levorotatory) configuration or may be a mixture of the two configurational varieties (e.g., d,l lactide). Polymers containing mixtures of d,l lactides possess little or no polymeric crystallinity resulting in lessened rigidity and a relatively low glass transition temperature when compared with a more crystalline counterpart such as l lactide. The preferred periodontal repair embodiment for the cell-barrier sheet material component contains copolymers d,l lactide with glycolide which correspondingly provides minimal rigidity and a glass transition temperature conducive to subsequent thermal bonding of the embodiment incorporating a fibrous matrix on both sides of the barrier material.

These copolymers bioabsorb through hydrolysis returning them to their original components which are subsequently expelled from or assimilated into the body. The in vivo longevity of a particular

juncture is shown at 44. A method of affixing the cell-barrier sheet material surface will be described below.

As shown by Figure 5A, the implantable bioabsorbable article of the present invention may also be made so that it incorporates a bioabsorbable suture 50 to make the securing of the article to adjacent anatomical structures as simple as possible. This embodiment is considered to be at the present time the best mode of the present invention for periodontal repair. This embodiment is made most simply by placing a suture into the fold of the two-sided article described in Figure 4C. The cross section of Figure 5B shows this in detail. Other embodiments incorporating an affixed bioabsorbable suture are also possible. One such alternative embodiment is shown by Figure 5C wherein a portion 52 of the cell-barrier material 12 is not covered by the fibrous matrix 10 and that portion 52 of the article is folded around a length of suture 50. The coronal edge of the article as implanted is indicated at 54. Other methods of attaching a suture may be used, for example, interweaving the suture through the thickness of the article.

In an alternative embodiment, the fibrous matrix, the fibers, the cell-barrier material, or any combination thereof may also be impregnated with any single or combination of substances such as antibiotics, antimicrobials, growth factors, differentiation factors, cell attachment factors or other such therapeutic agents. Impregnation of the implantable bioabsorbable article with such a therapeutic agent involves simply coating the article with the agent or alternatively incorporating the agent into the material from which either the fibrous matrix or the cell-barrier is constructed. For example, the therapeutic agent may be included in the polymer and solvent solution from which the cell-barrier is subsequently made. The incorporation of a therapeutic agent into the material of the implantable bioabsorbable article in this fashion would result in the release of the therapeutic agent into the living body in which the article is implanted. The presence of such an impregnating therapeutic agent in the implantable bioabsorbable article can be determined by accepted analytical techniques involving extraction, solvation, or other isolation methods whereby the therapeutic agent

heat at a temperature above the boiling point of the solvent in order to evaporate the solvent. The heating surface 72 must possess suitable release properties to allow removal of the finished implantable bioabsorbable article without damage. Suitable heating surface materials include polytetrafluoroethylene (PTFE), fluorinated ethylene-propylene (FEP), and other materials having adequate temperature capability and having release properties.

The preferred process for producing the implantable bioabsorbable article of the present invention is as follows. The fibrous matrix 10 and the solution of bioabsorbable polymer and solvent 70 are introduced between two opposing release surfaces 72 and 74 which are then compressed together as indicated by arrows 76 while heat in excess of the boiling temperature of the solvent is applied from release surface 72. The temperature should be higher than the boiling point of the solvent in order to assure rapid evaporation of the solvent within a few seconds. As a result of the rapid evaporation of the solvent, the fibrous matrix material is coated with the solvent carried polymer. Upon evaporation of the solvent, points of contact between adjacent fibers of the matrix are adhesively bonded. Simultaneously, the cell-barrier sheet material of the chosen bioabsorbable polymer or copolymer is deposited at the surface from which heat is applied. The resulting implantable bioabsorbable article is then removed from between the release surfaces.

To construct the two-sided embodiment shown by Figure 4B having a fibrous matrix on two the opposing surfaces of the cell-barrier sheet material, two implantable bioabsorbable articles are prepared as described above. The two implantable bioabsorbable articles are placed so that their cell-barrier surfaces face each other and are superimposed on each other laminarly as shown by Figure 8. Pressure and heat are applied at a temperature above the glass transition temperature of the barrier and below that of the fiber. This results in the two film surfaces adhering to one another to form a composite having a fibrous matrix on the two opposing surfaces of the cell-barrier sheet material. It is preferable to prepare the cell-barrier sheet materials with a PLA/PGA copolymer for the two-sided embodiment as the copolymer possesses a glass transition temperature between 40 and 60°C.

article of the present invention is capable of providing for the exclusion of adjacent tissues from the nerve repair site, the containment of proliferating nervous tissue, and the retention of neurotropic and neurotrophic factors in the vicinity of the proximal nerve end. In a preferred embodiment for nerve repair, a tube is made by rolling the implantable bioabsorbable article into a tubular form as previously described with the fibrous matrix on the inner surface of the tube. It is preferred that the fibers be of an organized configuration in the form of parallel fibers on the inner surface of the tube oriented parallel to the longitudinal axis of the tube. It is believed that this fiber orientation provides a directional aid to the healing of the nerve between exposed nerve ends. The proximal and distal ends of a transected nerve will be placed in respective ends of this tubular article. These nerve ends may be abutted and sutured together, simply abutted, or left with a gap between the nerve ends when the tubular article is finally sutured or affixed by any suitable means to the nerve sheaths of the two nerve ends.

As shown by the cross section of Figure 12, an alternative tubular embodiment for nerve repair incorporates a layer of randomly configured fibrous matrix 121 between the outer cell-barrier sheet material surface of the tube and the inner surface of parallel longitudinally oriented fibers 113. This construction offers improved crush resistance. The longitudinally oriented fibers 113 are shown in exaggerated diameter for clarity.

In another tubular embodiment, an additional fibrous matrix may be used on the outer surface of the tube if attachment and stabilization of the surrounding external tissue is desired. A further embodiment may use a fibrous matrix outer tube surface with the cell-barrier sheet material forming the inner surface of the tube.

The implantable bioabsorbable article of the present invention may also be useful for repair of bone defects and bone regeneration. Specific applications include endochondral bone, intermembranous or round bone, and long bone. The implantable bioabsorbable article may include a fibrous matrix laminarly affixed to only one side of the cell-barrier sheet material or will preferably include having a fibrous matrix affixed to both sides of the cell-barrier sheet

of an approximately 3 inch pass of the roller across the surface of the fibrous matrix at a rate of approximately one complete cycle (2 passes) per second for a total of 2 minutes. The application of heat and pressure resulted in a finished implantable bioabsorbable article having a fibrous matrix laminarly affixed to one side of a cell-barrier sheet. Upon completion, the two FEP film sheets 91 and 92 and the finished implantable bioabsorbable article contained between the two FEP sheets was removed from the heated aluminum plate and allowed to cool under passive pressure applied by a 4" x 4" x 1" aluminum block.

After cooling, the two sheets of FEP were peelably removed from the finished implantable bioabsorbable article. The finished article was trimmed to 15 mm width and a 30 mm length. The article was folded in half across its 15mm width with the cell-barrier surface on the inside. A 5-0 PGA suture obtained commercially was trimmed of its needle and placed into the fold of the material as shown by Figures 5A nad 5B. The folded article was placed between two FEP film sheets and compressed by the roller and heated plate apparatus described by Figure 8. The plate temperature was 100°C. Pressure was again applied by traversing the roller back and forth over the article in one second cycles for a total period of 1 minute.

The finished implantable bioabsorbable article having an integrally attached suture was placed into a food grade pouch made of a polymer foil laminate. The pouch was sealed and gamma radiation sterilized at a total dosage of 2.0 Mrad.

EXAMPLE 2

The implantable bioabsorbable articles made and sterilized according to Example 1, each article incorporating an integrally attached suture as shown by Figures 5A and 5B, were implanted in dogs. The dog model has been used extensively for the testing of guided tissue regeneration techniques and materials (Caffesse et al. 1988, J. Periodontal Vol 59, 589-584; Claffey et al. 1989, J. Clin. Periodontal, Vol 16, 371-379).

At surgery, buccal and lingual full-thickness muco-periosteal

combination of interrupted and vertical mattress sutures. Care was taken to make sure the membranes were completely covered by the soft tissue of the flaps.

The dogs received post operative oral hygiene care in the form of chlorhexidine (0.12%) flushes every other day starting seven days after surgery. Clinical parameters monitored during the healing period were gingival health, plaque index, exposure of material, gingival recession, and fragmentation or resorption of the exposed material.

Sacrifice times for the animals were 2, 4, 8 and 12 weeks postoperative. At the time of sacrifice, the experimental teeth were removed en bloc and placed in 70% ethanol/30% distilled water fixative. After fixation, the teeth were infiltrated and embedded in poly(methylmethacrylate) and fifteen 6-8 micron thick bucco-lingual sections spanning the mesio-distal width of each tooth were cut for histological evaluation with a Reichart-Jung Polycut S sledge microtome. One section representing the greatest length of each root and located as close to the furcation as feasible was chosen for evaluation. The parameters measured on each root available for evaluation were:

Apical Epithelial Migration (EM) - the distance from the apical extent of the epithelium to the gingival margin.

New Bone (NB) - the distance from the base of the instrumented root surface to the coronal extent of the new regenerated bone.

New Cementum (NC) - distance from the base of the instrumented root surface to the coronal extent of regenerated new cementum.

Defect Depth (DD) - the base of the instrumented root surface to the gingival margin (the area "at risk" for regeneration).

For EM, NB and NC, the distances were divided by DD and multiplied by 100 to obtain a percentage of the defect depth. The values for all available roots for each dog were averaged to obtain a single value for each dog. No adequate sections were obtained for three roots of the 4 week dog, 1 root of the 8 week dog and three roots of the 12 week dog.

Concurrently, protection of the defect space from the epithelium and the gingival connective tissue by the implantable bioabsorbable articles allowed the regeneration of new bone in the defect space and new cementum on the root surfaces.

EXAMPLE 3

The preferred embodiment currently utilizes d,l PLA:PGA copolymer ratios between 50:50 and 85:15 for the cell-occlusive barrier forming material to provide a desirable in vivo bioabsorption rate for the periodontal application. Examples of the preferred embodiment were fabricated in accordance with the description of Example 1 with the following exceptions:

A. Approximately 38 to 42 milligrams of approximately 25 micrometer diameter PGA staple fibers were utilized in the fabrication of the fibrous matrix.

B. Individual samples were made utilizing d,l PLA:PGA copolymer ratios of either 85:15, 75:25, 60:40, and 50:50 for the cell-occlusive barrier forming material.

C. Each of the preferred embodiments utilizing d,l PLA:PGA copolymer ratios of either 85:15, 75:25, or 60:40 were fabricated with an approximately 1:3 to 1:5 (w/w) solution of the respective copolymer in acetone instead of in methylene chloride as described in Example 1.

EXAMPLE 4

A tubular article useful for tissue repair such as, for example, nerve repair, was constructed as follows.

A group of 1.5 inch long, 30 micron diameter PGA fibers were laid out approximately parallel in a strip about 0.5 inch wide, thus forming a fibrous matrix of organized configuration. 0.2 grams of about 1:5 (w/w) solution of 85:15 PLA:PGA copolymer in acetone was placed on this strip of fibers and heated and compressed in the apparatus of Figure 8 in the same manner as described in Example 1. The resulting implantable bioabsorbable article having a fibrous matrix of approximately parallel fibers was then trimmed to a

I CLAIM:

1. An implantable bioabsorbable article useful for the separation and regeneration of mammalian tissue comprising:
   a) a bioabsorbable cell-barrier sheet material having first and second opposing surfaces; and
   b) a bioabsorbable fibrous matrix laminarly affixed to the first opposing surface of said bioabsorbable cell-barrier sheet material;

   wherein said fibrous matrix allows the ingrowth of tissue into the fibrous matrix and said bioabsorbable cell-barrier sheet material substantially precludes the passage and further ingrowth of tissue, thereby separating the ingrowth of tissue into the fibrous matrix adjacent to the first opposing surface of the cell-barrier sheet material from the regeneration of tissue adjacent to the second opposing surface of the cell-barrier sheet material.

2. An implantable bioabsorbable article according to Claim 1 wherein the bioabsorbable fibrous matrix is laminarly affixed to the first and second opposing surfaces of said bioabsorbable cell-barrier sheet material.

3. An implantable bioabsorbable article of Claim 1 wherein both the cell-barrier sheet material and the fibrous matrix are comprised of a synthetic bioabsorbable material selected from the group consisting of polylactic acid, polyglycolic acid, poly-P-dioxanone, trimethylene carbonate, polycaprolactone and copolymers thereof.

4. An implantable bioabsorbable article of Claim 3 wherein both the cell-barrier sheet material and the fibrous matrix are comprised of a copolymer of polylactic acid and polyglycolic acid.

5. An implantable bioabsorbable article of Claim 3 wherein the cell-barrier sheet material is comprised of a copolymer of polylactic acid and polyglycolic acid and the fibrous matrix is comprised of polyglycolic acid fibers.

6. An implantable bioabsorbable article of Claim 5 wherein the cell-barrier sheet material is comprised of a copolymer of about 50% polylactic acid and 50% polyglycolic acid.

article having a fibrous matrix laminarly affixed to a cell-barrier sheet material, comprising:

a) making an incision between gingival tissue and a periodontal defect;

b) placing the implantable bioabsorbable article into the incision so that it separates the gingival tissue from the periodontal defect in order to allow for the regeneration of periodontal tissue without interference from the gingival tissue, the implantable bioabsorbable article being placed with the fibrous matrix adjacent to the gingival tissue; and

c) closing the incision.

18. A method of using an implantable bioabsorbable article to repair a bone defect, said implantable bioabsorbable article having a fibrous matrix laminarly affixed to a cell-barrier sheet material, comprising:

a) exposing the bone defect;

b) placing the implantable bioabsorbable article over the bone defect to separate the bone defect from adjacent tissue and to preserve space proximal to the bone defect, the fibrous matrix being placed against the adjacent tissue; and

c) securing the implantable bioabsorbable article over the bone defect.

19. A method of using an implantable bioabsorbable article to prevent a soft tissue adhesion from occurring on a soft tissue surface, said implantable bioabsorbable article having a fibrous matrix laminarly affixed to a cell-barrier sheet material, comprising placing the implantable bioabsorbable article on the soft tissue surface where the soft tissue adhesion is likely to occur.

20. A method of using an implantable bioabsorbable article to aid in repair of nerve ends, said implantable bioabsorbable article having a fibrous matrix laminarly affixed to a cell-barrier sheet material and said implantable bioabsorbable article being in the form of a tube having open ends, comprising:

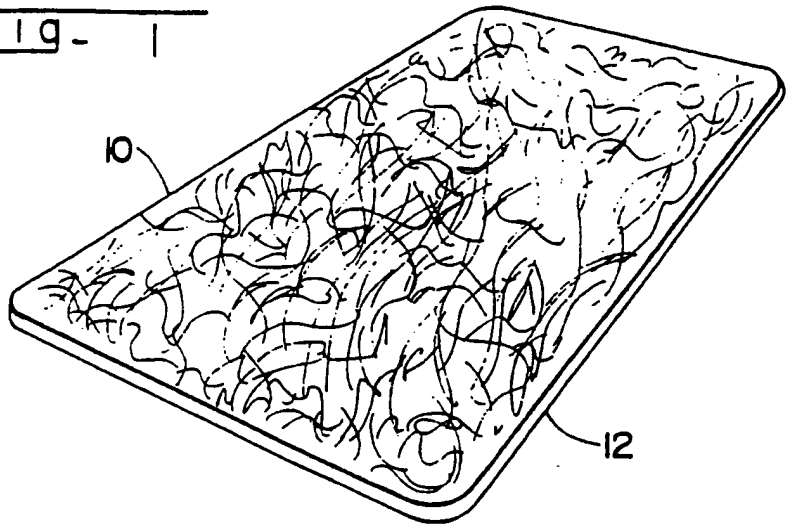
a) making an incision to expose the nerve ends;

b) placing the nerve ends into the open ends of the tube;

c) affixing the tube to the nerve ends by affixing means; and

d) closing the incision.

Fig - 1



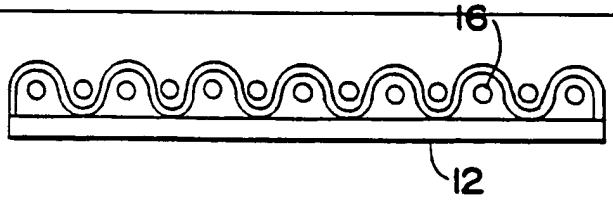


Fig - 3

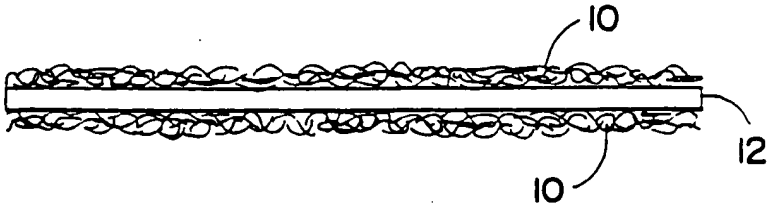


Fig - 4a

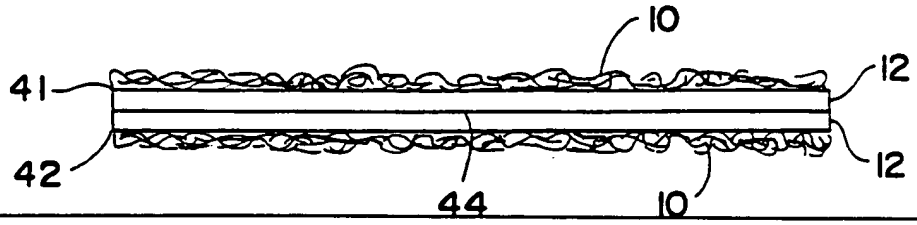


Fig - 4b

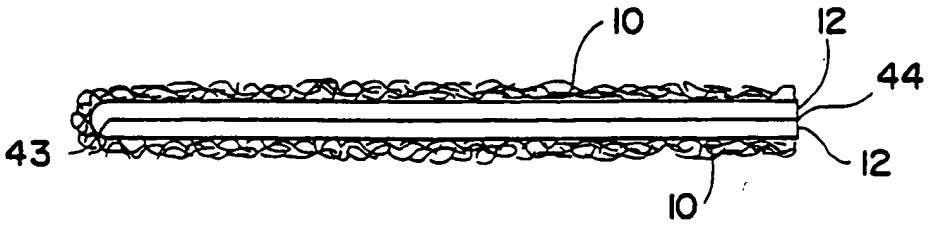


Fig - 4c

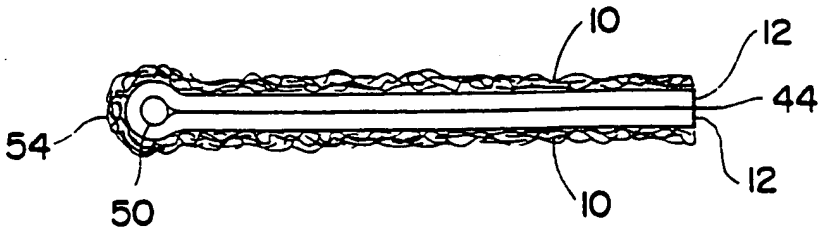


Fig- 5b

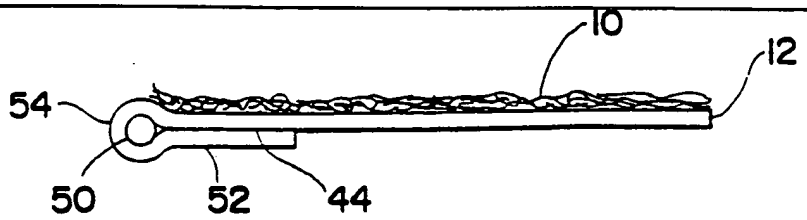
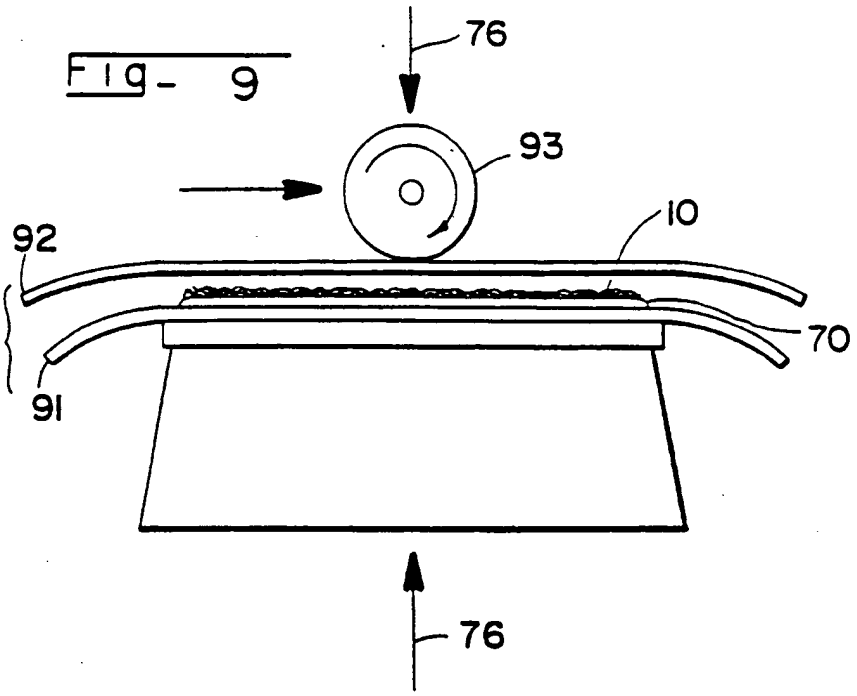


Fig- 5c

Fig- 9



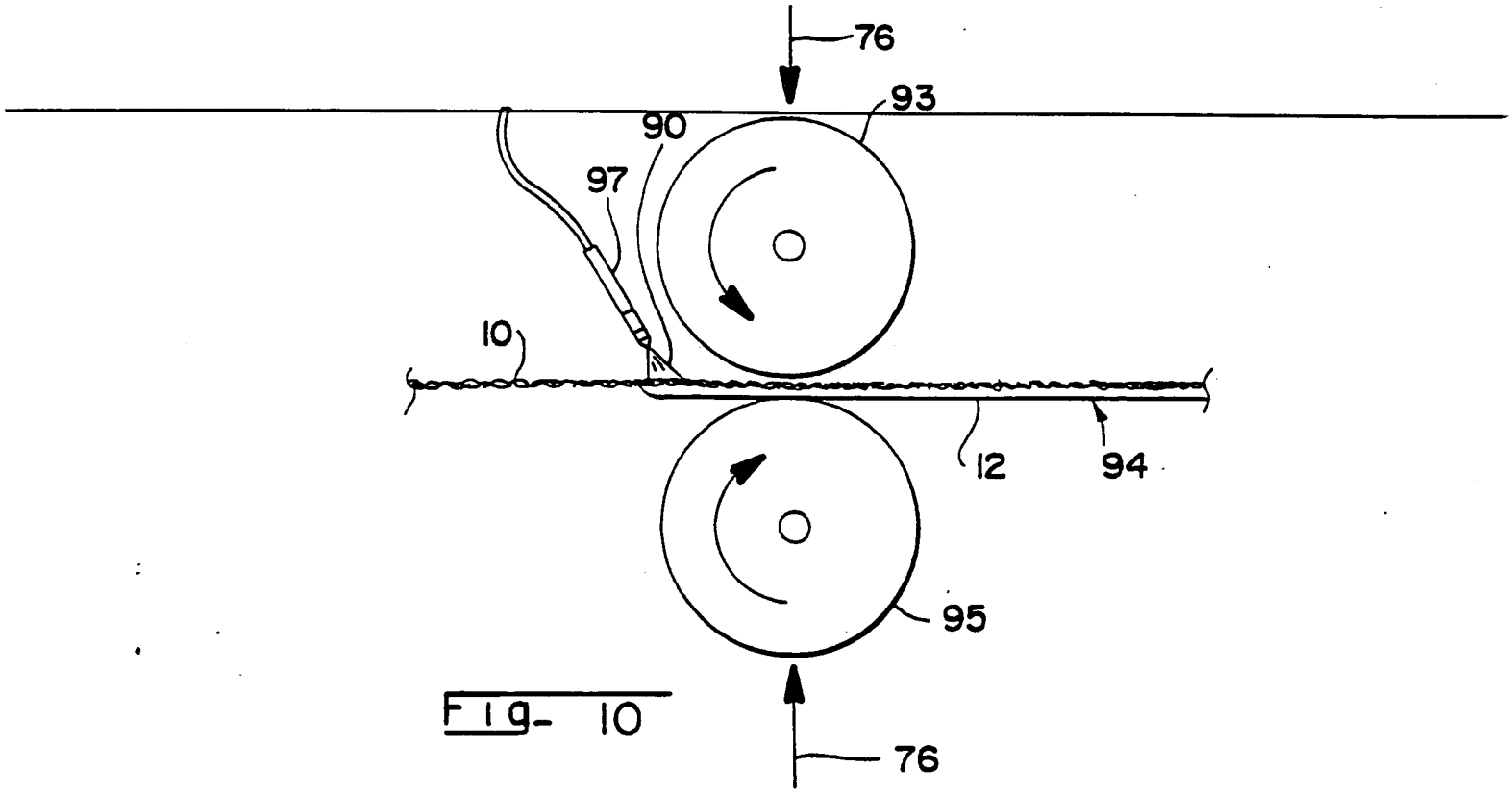


Fig- 10

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/08972

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)*

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 L 27/00 A 61 L 31/00 A 61 F 2/28
A 61 B 19/00 A 61 B 17/11

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO,A,9000410 (BIOCON OY) 25 January 1990, see claims 1-13 ---	1-16
X	WO,A,8805312 (MATERIALS CONSULTANTS OY) 27 July 1988, see claims ---	1-16
X	EP,A,0274898 (ETHICON INC.) 20 July 1988, see page 3, lines 8-13; claims 1-10 ---	1
A	FR,A,2635966 (ETHICON, INC.) 9 March 1990 ---	
A	WO,A,9013302 (BRIGHAM AND WOMEN'S HOSPITAL) 15 November 1990 ---	
A	US,A,4870966 (A.L. DELLON et al.) 3 October 1989 (cited in the application) --- -/-	

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06-04-1992	15. 05. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Daniell van d r Haas

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 17-20 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

Please see rule 39.1(iv)

2. [ ] Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the international application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.